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10/516,553	11/30/2004	Tadaaki Yabubayashi	09853/0202140-US0	7061
7278	7590	11/13/2007	EXAMINER	
DARBY & DARBY P.C. P.O. BOX 770 Church Street Station New York, NY 10008-0770			POHNERT, STEVEN C	
			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/516,553

Applicant(s)

YABUBAYASHI ET AL.

Examiner

Steven C. Pohnert

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1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 11-14 and 23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 11-14 and 23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 November 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

This action is in response to papers filed 8/27/2007.

The papers of 8/27/2007 amended claims 1 and 4 to require the labels of claim 10 and claim 10 was canceled.

The amendment has overcome the 112-2nd rejections of claims 1-9 and 11-14 directed to "detecting/discriminating."

The amendment has also overcome the 112-2nd paragraph rejections of claims 1 and 6 due to lack of antecedent basis.

The 112-2nd paragraph rejection of claim 10 has been overcome as claim 10 has been canceled.

The 102 and 103 rejections based on the teachings of Cass has been overcome by the amendment of claims to require, " wherein the label is selected from the group consisting of fine metal particles, fine Si particles, magnetic particles, ceramic fine particles and semiconductors."

The 102 rejections based on the teachings of Gold has been overcome by the amendment of claims to require, " wherein the label is selected from the group consisting of fine metal particles, fine Si particles, magnetic particles, ceramic fine particles and semiconductors."

The following presents new grounds of rejection necessitated amendment of claims 1-9 and 11-14 and 23.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-9, 11-14 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9, 11-14 and 23 recite, "hybridizing a biochemical specimen with a nucleic acid probe on a biochip, the nucleic acid probe including a configuration of a loop structure and arrayed on one or more electrodes provided on a surface of a substrate or substrate analog or the nucleic acid probe with said configuration but further including a modification added in advance with a label; and". It isn't clear as to whether the modification comprises adding a label or if the probe is modified in some manner and prior to or subsequent to the modification a label is added etc. Further it is unclear if the claim could also be requires either just the nucleic acid probe with the loop structure and arrayed on the electrode or a nucleic acid with the configuration and further including a modification with a label It is unclear if the claim requires a modified probe that is attached to an array or a probe that is attached to an array that is subsequently modified.

3. Claim 23 recites the limitation "the modification operation" in the third line. There is insufficient antecedent basis for this limitation in the claim. "modification operation" has not been previously recited in the claims. This rejection can easily be overcome by amending the claim "after modifying with a label."

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1-9, 11-14 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al (WO/1999/31275, Published June 24, 1999) in view of Blackburn et al (US Patent 6264825 issued July 24, 2001).

With regards to claims 1 and 2, Gold et al teach teaches the use of mutually complementary nucleic acids for detection of binding of a target molecule to a nucleic acid ligand (see page 20, lines 26-30). Gold teaches the detection of ligand binding by electronic means (see abstract) and further teaches the use of gold or silver as the substrate for the array (see page 12, line 30). Thus the gold or silver of Gold allow for detection by the transfer of electrons and thus are electrodes (see page 26, lines 7-31). Gold further teaches, " an insulative silica "gate" is placed between two n-type semiconductors, forming a biochip. Current will flow from one semiconductor to the other when a conducting channel is formed in the gate and a potential difference is applied" (see page 26, lines 9-14). Gold et al teaches a target molecule is a nucleic acid (see page 6, lines 11-15). Gold further teaches that upon targeting molecule

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binding to the nucleic acid ligand a conformation change occurs that allows hybridization of further nucleic acid molecules to the nucleic acid ligand (page 20, lines 28-30). Gold teaches the nucleic acid molecules further modifying the nucleic acid ligand also undergo a conformational change allowing the formation of an intermolecular hybridization complex to form (see page 20, line 30-page 21, line 5). Gold further teaches the mutually complementary nucleic acids are stem-loop nucleic acids (see page 21, lines 15-16). Gold further teaches that scaling up of technology accurately allows the measurement of thousands of discrete changes in current drain (see page 26, line 23).

With regards to claims 3 and 4, Gold teaches the use of nucleic acids with a fix sequence surrounding a randomized region. These fixed regions are labels.

With regards to claim 5 and 6, Gold teaches binding of the target molecule results in a net loss or gain of ions at that region of the chip, altering conductance and a current drain in this area of the chip (see page 26, lines 16-22). Gold's teaching of detecting alterations in current conductance after the addition of a target ligand inherently requires that the conductance before addition of the ligand is known. Gold thus teaches the detection and quantification before and after hybridization.

With regards to claims 8 and 9, Gold teaches the thiolpropionate having a photochemical reactive group is couple to functional groups on the surface of the biochip (see page 13, lines 8-10). Gold further teaches light of the appropriate wavelength, followed by the attachment to substrate (see page 13, lines 10-16) and the

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unbound nucleic acid is washed away. Gold further teaches the use of photoactivatable biotin (label) by a similar method (see page 13, lines 23-25).

Gold does not teach the label is a fine metal particle, or magnetic particle (claims 1 and 3). Gold does not teach the labeling of a biochemical sample in advance of hybridization (claims 3). Gold et al does not detection of the probes on each electrode prior to the hybridization with the biochemical reactant (claim 7). Gold et al does not teach detection of complex by electronic methods (claim 11). Gold et al does not teach detection/discrimination of the complex by electronic and magnetic methods (claim 12). Gold et al does not teach detection by electronic and optical methods (claim 13). Gold et al does not teach detection by magnetic, optical and electronic means (claim 14).

However, Blackburn et al teaches a method of detecting an analyte by electron transfer moiety (ETM) (see abstract). Balckburn teaches that the ETM are labeled nucleic acids containing transition metals (see column 45, lines 9-20). Blackburn et al further teaches the use of silicon containing moieties as labels (see column 27, line 1). Blackburn et al teaches the detection of the use of a plurality of gold electrodes (see column 2, lines 60-65). Blackburn further teaches the detection of probes prior to any experiment for use as an internal control for calibration of an experiment (see column 48, lines 4-14) (claim 7). Blackburn teaches the enzymatic incorporation of an ETM (label) during PCR (see column 60, lines 8-11) (claim 3 and 4, biochemical probe modified in advance). Blackburn et al further teaches the detection of the presence of ETM on the surface of the electrodes by amperometry, voltametry, capacitance or impedance (see column 81, lines 55-67) (claim 11).

With regards to claim 12, Blackburn teaches the use of magnetic particles can be used to associate the ligand complex with the detection electrode, thus allowing detection/discrimination comprising magnetic and electronic methods (see column, 19, lines 33-39). Thus Blackburn's use of magnetic particles to selectively move the ligand complex to the electrodes where it is detected results in detection based on discrimination (movement on magnetic particles) and detection by electronic means at electrode.

With regards to claim 13, Blackburn teaches detection of the presence of the ETM on the surface of the detection electrode by use of electrochemiluminescence (see column 80, line 47). Electrochemiluminescence is activation of chemiluminescence by a current. Thus the increase in the current results in detection of an optical signal.

With regards to claim 14 and 23, Blackburn teaches the use of magnetic particles used to associate the ligand complex with the detection electrode, thus allowing detection/discrimination comprising magnetic and electronic methods (see column, 19, lines 33-39). Further, Blackburn teaches detection of the presence of the ETM on the surface of the detection electrode by use of electrochemiluminescence (see column 80, line 47). Electrochemiluminescence is activation of chemiluminescence by a current. Thus the increase in the current results in detection of an optical signal. Thus Blackburn teaches the detection/discrimination of a chemical reactant complex comprising the use of discriminating on magnetic signal, current values and optical. Thus Blackburn teaches detection of electrical and optical changes before and after hybridization.

Therefore it would have been prima facie obvious to one of ordinary skill in art at the time the invention was made to combine the hairpin probes of Gold with detection method of Blackburn, including Blackburn's metal and silicon containing labels. The skilled artisan would be motivated because Blackburn teaches his method allows concentration of the target ligand with the capture ligand maximizing interaction (see column 9, lines 37-40). The ordinary artisan would further be motivated as this allows very small samples to be analyzed (see column 81, lines 25-27). The ordinary artisan would be motivated to use Blackburn's method of internal control as it allows more accurate and quantitative detection. Thus the combined teachings of Gold and Blackburn would result in the ability to increase the sensitivity of the loop probes of Blackburn by concentrating the biochemical samples with the probes. The combined teachings would also allow for improved sensitivity because the quantization of the probes would result in a better determination of the limits of detection of the assay.

Response to Arguments

The response of 8/27/2004 asserts on page 9 that, " Neither Cass, Gold or Blackburn teach, suggest or provide motivation to use the labels recited in amended claims 1-4." This argument has been thoroughly reviewed but is not considered persuasive because Blackburn does teach the use of labels containing metal and silicon as the modified rejection depicts.

The instant rejection meets each and every limitation of claims 1-9, 11-14 and 23.

Summary

No claims are allowed.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

A handwritten signature in black ink, appearing to read "St Pohnert", written in a cursive style.

Steven Pohnert

/Carla Myers/
Primary Examiner, Art Unit 1634